

Title: Protected vial, and method for manufacturing same

The invention relates to a method for manufacturing a protected vial and to a protected vial which can be manufactured according to this method.

Vials are frequently used in medical practice. Usually, vials consist of a container filled with a medicinal fluid, and are sealed with a seal which can be pierced with a hypodermic needle. The vial is often also provided with a protective cap which needs to be removed before use. In the process of producing these vials, there is a considerable chance of medicinal fluid ending up on the outside of the vial. Therefore, after filling and sealing, the vials are rinsed in order to remove this fluid. However, it is known from practice that the outside of a vial is not always clean, i.e. free from contamination with an active substance. In that case, rinsing has not led to complete removal, and still traces of the active substance have remained.

Often, the fact that traces of an active substance remain does not constitute a problem, but in certain cases, such as for example in the case of cytostatics and antibiotics, this is different. For instance, it is known that cytostatics can absorb on glass. This may cause hospital and pharmacy employees, in dealing with such vials, to undesirably get in contact with these possibly highly toxic substances. In the case of antibiotics, contamination on the outside is undesirable, because this may lead to faster resistance of micro-organisms against the antibiotics concerned when these micro-organisms get in contact with the vial, or when the antibiotics concerned get in contact with micro-organisms carried by hospital and pharmacy employees.

An important objective of the present invention is to cancel the above-mentioned disadvantages and thereby preventing its negative consequences. To that end, the present invention provides a method for manufacturing a protected vial, wherein a tight-fitting envelope is arranged around a vial after its filling, wherein a bottom sticker is arranged

against a bottom of the vial, and wherein subsequently a tight-fitting sleeve is arranged over at least the entire side wall of the vial, while partly overlapping the bottom sticker along a circumferential edge of the bottom.

As a result, a possible contamination which remains on the outside of the vial after rinsing the vial is encapsulated between the vial and the tight-fitting envelope, which is arranged on the vial in two parts, namely a bottom sticker and a tight-fitting sleeve. Hereby, a user is no longer exposed to toxic substances, because the user will not touch the vial itself, but will touch the envelope. Because the envelope fits tightly around the vial, one keeps the normal physical "feeling" with the vial during use, so that its further handling and processing remains the same. With regard to developing resistance, micro-organisms now do not get a chance to get in contact with traces of antibiotics on the outside of the vial. An additional advantage is that if a vial breaks, the envelope will still take care of holding the pieces of glass together, and possibly the fluid is prevented from leaking away.

The application of a protective envelope takes place after filling the vial; preferably after the step of sealing the vial has taken place as well.

Preferably, the bottom sticker is self-adhesive, and is stuck on the bottom of the vial. In a preferred embodiment of the invention, the tight-fitting sleeve, which is part of the tight-fitting envelope, and which serves for covering at least the entire side wall of the vial, is manufactured from a synthetic material. This sleeve has been slid over the vial with little space and has shrunk under application of heat, and is thereby fitted tightly around the vial.

It is noted that a method for arranging a tight-fitting envelope around a vial is known from US 3 826 059. According to the known method, a filled and sealed vial is placed in a synthetic envelope, which is shrunk on the vial under the influence of heat. The envelope comprises a bottom part for covering the bottom of the vial, and an upstanding cylindrical

part for covering the side wall of the vial and a portion of a protective cap that is positioned on the vial.

According to the known method, the envelope is arranged around the vial as one piece, which constitutes an essential difference with respect to the method according to the present invention, given the fact that according to the latter method, the envelope is provided in two pieces, namely a bottom sticker and a sleeve. An important advantage of doing so is that the process of arranging the envelope around the vial is simplified. Also, it is easier to manufacture bottom stickers and cylindrical sleeves than an envelope having a bottom part and a cylindrical part extending from the bottom part. Moreover, when the known method is applied, the vial is pushed into an envelope which is closed at one end, which is more difficult than pulling a sleeve over the vial, as air needs to be pushed from the envelope, while there is little room for air to escape. Furthermore, there is a chance of air getting entrapped between the envelope and the vial when the envelope is shrunk on the vial. These disadvantageous effects do not occur when the envelope is arranged in two steps, wherein a first step comprises attaching the bottom sticker to the bottom of the vial, and wherein a second step comprises positioning the sleeve around the vial and shrinking the sleeve on the vial, wherein the sleeve is positioned such that it covers the side wall of the vial and partly overlaps the bottom sticker along a circumferential edge of the bottom of the vial.

The various aspects, features and advantages of the present invention will be further explained by the following description with reference to the attached drawing, in which:

- figure 1 shows a cross section of a protected vial according to the present invention, and
figures 2A-E schematically illustrate the successive steps of manufacturing of the protected vial of figure 1.

In figure 1, a cross section is shown of a filled and sealed protected vial 1 according to the present invention.

The protected vial 1 consists of a glass vial 2 known per se with a side wall 201, a bottom 202 and an access opening 3. In the vial 2, a medicinal fluid 7 is present. The protected vial 1 is provided with a pierceable sealing member 4, for example of rubber, and a protective cap 5, for example of metal.

On the outside of the vial 2, an envelope 6 is fitted tightly over almost the entire vial 2, leaving the protective cap 5 free. The envelope 6 comprises a bottom sticker 602 which covers the bottom 202 of the vial 2, and a sleeve 601 which covers the side wall 201 and partly overlaps the bottom sticker 602 along a circumferential edge of the bottom 202.

Preferably, the sleeve 601 is made of a transparent synthetic material, for example a film of PE, PP, PVC or the like. Furthermore, it is preferable that the bottom sticker 602 is manufactured from a transparent synthetic material as well. Also, it is preferable that the bottom sticker 602 is self-adhesive, but this is not necessary within the scope of the invention.

A suitable value for the thickness of the sleeve 601 is 0.05 mm; but the value for the thickness may also be higher or lower. Preferably, the bottom sticker 602 has a thickness in the order of approximately 0.15 mm. For sake of clarity, in figure 1, some parts of the protected vial 1 are shown in an exaggeratedly thick fashion.

The protected vial 1 is manufactured in steps which are described in the following and which are illustrated in the figures 2A-E, in a simplified way. At first an empty vial 2, known per se, is provided (figure 2A). Then, this vial 2 is filled with a medicinal fluid 7, through the access opening 3 (figure 2B). Subsequently, a sealing member 4 is attached to the access opening 3 and a protective cap 5 is attached (figure 2C). Then, the whole is rinsed in order to remove the fluid which has possibly been spilt on the outside of the vial 2 during filling. Subsequently, a synthetic bottom sticker 602 is attached to the bottom 202 of the vial 2, and a synthetic sleeve 601 is slid over the vial 2 (figure 2D). As last step, the sleeve 601 is subjected to a heat treatment, in such a way

that it shrinks and thereby becomes fitted tightly around the vial 2 (figure 2E).

In order to investigate the effect of providing vials 2 with a sleeve 601 and a bottom sticker 602 on an outside contamination of the vials, tests have been performed (Report for Pharmachemie BV, Haarlem, The Netherlands, by Exposure Control BV, Wijchen, The Netherlands and University Medical Center Nijmegen, Nijmegen, The Netherlands), during which the outside contamination of protected vials 1 and unprotected vials 2 containing cisplatin was measured. Extracts from the outside of the vials were destructured into platinum and analyzed with stripping voltametry (Metrohm Application Bulletin No. 220/1. Determine of ultratrace levels of platinum by stripping voltametry). Details of the tests are presented in the following table.

Batch	Vials without protection	Protected vials
Number of vials	7566	4067
Cisplatin (mg)	25	50
Volume cisplatin (ml)	50	100
Cisplatin (mg/ml)	0.5	0.5
Surface area (cm ²)	120	180
Extraction volume (ml HCl)	70	300

The tested vials were put in a single container. The containers were filled with 0.5 M HCl until the vials were completely immersed. The containers were closed, and after ultrasonification for 30 minutes, the vials were removed from the containers. During ultrasonification, cisplatin contamination on the outside of the vials was assumed to be dissolved in the HCl solvent.

Sample pre-treatment and analysis with stripping voltametry was performed according to standard procedures. One ml of the cisplatin extract was destructured into a platinum-complex using hydrogen peroxide, formaldehyde and UV-light, resulting in the formation of platinum (Pt). It is a known fact that cisplatin contains about 65% platinum. Analysis of platinum was performed in triplicate with a relative standard

deviation of 2-3%. The limit of detection was 10 ng/l of extract. Samples were diluted and reanalyzed in case high concentrations were encountered. Ten blank samples (empty vials) were extracted, analyzed and compared to the cisplatin vials to correct for background values of platinum (50 ng/l extract).

Values of absolute amounts of contamination found on the vials (Pt-abs) were compared between the protected vials 1 and the unprotected vials 2 with a Wilcoxon test. This test was also applied on the values of contamination per area surface (Pt-area), the values of contamination related to the contents of the vial (Pt-ratio out/in) and to all values corrected for blanks. P-values of 0.05 or less were considered significant. Data were characterized by median, range and quartiles.

Results of the tests are presented in the following table.

Batch	Unprotected vials			Protected vials		
	Pt-abs (ng)	PT-area (ng/cm ²)	Pt-ratio out/in (x10 ⁻⁶)	Pt-abs (ng)	PT-area (ng/cm ²)	Pt-ratio out/in (x10 ⁻⁶)
Min	3	0.02	0.17	BV*	BV*	BV*
Max	79	0.66	4.85	146	0.81	4.49
Median	7	0.06	0.43	4	0.02	0.11

* BV = Background Values

It is clear from the above table, in particular from the median data, that all parameters are significantly lower for the protected vials 1 compared to the unprotected vials 2. This proves that providing the vial 2 with an envelope 6 leads to a significant reduction of the outside contamination of the vial 2.

In order to investigate the effect of providing vials 2 with a sleeve 601 and a bottom sticker 602 on risks associated with accidental dropping of the thus obtained protected vials 1, drop tests have been performed (Report for Pharmachemie BV, Haarlem, The Netherlands, by Topa Instituut, Voorhout, the Netherlands; report number T04-1068). The applied test procedure consists of the following parts:

1) drop test from drop height of 120 cm

This test has been performed to simulate the accidental dropping of protected vials 1 from a table on a hospital floor. The drop height is 120 cm on random positions of the vials 1 (top, bottom or side). The surface on which the drops have taken place is a "Linoleum" plate, which simulates a hospital floor. Five drops have been performed with three different types of vials, namely 10ml vials, 50ml vials and 100ml vials.

2) drop test from drop height of 185 cm

This test has been performed to see what happens if the protected vial 1 falls from a shelf on a hospital floor. The drop height is 185 cm on random positions of the vials 1 (top, bottom or side). The surface on which the drops take place is the above-mentioned "Linoleum" plate.

The results of the drop test from the drop height of 120 cm are presented in the following table. For sake of completeness, it is noted that, in the table, the protected vials 1 are indicated as vials with cover, whereas unprotected vials 2, i.e. vials 2 without an envelope 6, are indicated as vials without cover.

		Drop height 120 cm					
		10ml vials		50ml vials		100ml vials	
		With cover	Without cover	With cover	Without cover	With cover	Without cover
		Results	Results	Results	Results	Results	Results
Drop on bottom	1	ok	ok	ok	ok	ok	ok
	2	ok	ok	ok	ok	ok	ok
Drop on top	1	ok	ok	ok	ok	ok	ok
	2	ok	ok	ok	ok	ok	ok
Drop on side	1	ok	ok	ok	ok	ok	ok
Total % intact		100%	100%	100%	100%	100%	100%

The results of the drop test from the drop height of 185 cm are presented in the following table.

		Drop height 185 cm					
		10ml vials		50ml vials		100ml vials	
		With cover	Without cover	With cover	Without cover	With cover	Without cover
		Results	Results	Results	Results	Results	Results
Drop on bottom	1	ok	ok	ok	ok	ok	ok
	2	ok	ok	ok	ok	ok	ok
	3	broken	ok	ok	ok	ok	ok
	4	ok	ok	ok	ok	broken	ok
	5	ok	ok	ok	ok	ok	ok
	6	ok	ok	ok	ok	-	-
	7	ok	ok	ok	ok	-	-
	8	ok	broken	ok	ok	-	-
	9	ok	ok	ok	ok	-	-
	10	ok	ok	ok	ok	-	-
Drop on top	1	ok	ok	ok	ok	ok	ok
	2	ok	ok	ok	ok	ok	ok
	3	ok	ok	ok	ok	ok	ok
	4	ok	ok	ok	ok	ok	ok
	5	ok	ok	ok	ok	ok	ok
	6	ok	ok	ok	ok	-	-
	7	ok	ok	ok	ok	-	-
	8	ok	ok	ok	ok	-	-
	9	ok	ok	ok	ok	-	-
	10	ok	ok	ok	ok	-	-
Drop on side	1	ok	ok	broken	broken	broken	broken
	2	ok	ok	cracked	ok	broken	broken
	3	ok	ok	ok	broken	broken	broken
	4	ok	ok	ok	ok	broken	broken
	5	ok	ok	ok	ok	broken	broken
	6	ok	ok	ok	broken	cracked	ok
	7	ok	ok	cracked	ok	cracked	broken
	8	ok	ok	cracked	ok	ok	broken
	9	ok	ok	ok	ok	cracked	broken
	10	ok	ok	ok	ok	broken	broken
Total % intact		96,7%	96,7%	86,7%	90,0%	50,0%	50,0%

From the results of the drop tests, it is concluded that providing a vial 2 with a sleeve 601 and a bottom sticker 602 does not lead to an improved protection of the vials 2 against breakage. However, it has appeared that if such a vial 2 sustains damage, the vial 2 often gets cracked rather than broken. Furthermore, it has appeared that if such a vial 2 breaks or cracks, in 50% of these cases, the vial 2 still contains its contents. In all cases of breakage of an unprotected vial 2, the contents are spilled over the floor. Therefore, the conclusion is justified that the application of the sleeve 601 and the bottom sticker 602 leads to a safer handling of the vials.

The above-described embodiment is merely an illustration of the possibilities of the present invention. Several modifications and adjustments are possible within the scope of protection of the invention as defined by the attached claims.

The present invention is summarized as follows. For the prevention of contamination of a vial 2 with traces of medicinal fluids, for example cytostatics and antibiotics, which may be spilt on the outside of the vial 2 while filling, the vial 2 is provided with a tight-fitting protective envelope 6 as a last step in the production process. The envelope 6 comprises a bottom sticker 602 which is attached to a bottom 202 of the vial 2 and a tight-fitting sleeve 601, which is shrunk on a side wall 201 of the vial 2, while partly overlapping the bottom sticker 602 along a circumferential edge of the bottom 202 of the vial 2. As a result of the arrangement of the envelope 6, a possible contamination which remains on the outside of the vial 2 is encapsulated between the vial 2 and the envelope 6. Consequently, a user is no longer exposed to toxic substances, because the user will not touch the vial 2 itself, but will touch the envelope 6. An additional advantage of the provision of the envelope 6 is that if breaking of the vial 2 occurs, the envelope 6 will keep the pieces of broken glass together and will possibly prevent the medicinal fluid 7 from leaking away.

CLAIMS

1. Method for manufacturing a protected vial, comprising the steps of:

- providing a vial with a side wall, a bottom and an access opening;

- filling the vial with a medicinal fluid;

- attaching a sealing member to the access opening;

- arranging a tight-fitting envelope around the vial,

after the step of filling the vial has taken place, wherein a bottom sticker is arranged against the bottom of the vial, and

wherein subsequently a tight-fitting sleeve is arranged over at least the entire side wall of the vial, while partly overlapping the bottom sticker along a circumferential edge of the bottom.

2. Method according to claim 1,

wherein the step of arranging the envelope takes place after the step of attaching the sealing member.

3. Method according to claim 1 or 2,

wherein a protective cap is attached to the sealing member.

4. Method according to claim 3,

wherein, during the process of arranging the envelope, the protective cap is left free.

5. Method according to any of claims 1-4,

wherein the sleeve is manufactured from a synthetic material, and is slid over the vial with little space, and wherein subsequently a heat treatment is performed, in such a way that the sleeve shrinks, thereby fitting itself tightly around the vial.

6. Protected vial, comprising a filled and sealed vial having a side wall and a bottom,

wherein a tight-fitting envelope is arranged around the filled and sealed vial,

and wherein the envelope comprises a tight-fitting sleeve and a bottom sticker, wherein the bottom sticker is arranged against the bottom of the vial, and wherein the sleeve is arranged over at least the entire side wall of the vial, while partly overlapping the bottom sticker along a circumferential edge of the bottom.

7. Protected vial according to claim 6,

wherein the vial is manufactured by the method according to any of claims 1-5.